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COMMENTARY

How Does a Specific Learning and Memory System in the Mammalian Brain Gain Control of Behavior?

Robert J. McDonald* and Nancy S. Hong

ABSTRACT: This review addresses a fundamental, yet poorly understood set of issues in systems neuroscience. The issues revolve around conceptualizations of the organization of learning and memory in the mammalian brain. One intriguing, and somewhat popular, conceptualization is the idea that there are multiple learning and memory systems in the mammalian brain and they interact in different ways to influence and/or control behavior. This approach has generated interesting empirical and theoretical work supporting this view. One issue that needs to be addressed is how these systems influence or gain control of voluntary behavior. To address this issue, we clearly specify what we mean by a learning and memory system. We then review two types of processes that might influence which memory system gains control of behavior. One set of processes are external factors that can affect which system controls behavior in a given situation including task parameters like the kind of information available to the subject, types of training experience, and amount of training. The second set of processes are brain mechanisms that might influence what memory system controls behavior in a given situation including executive functions mediated by the prefrontal cortex; switching mechanisms mediated by ascending neurotransmitter systems, the unique role of the hippocampus during learning. The issue of trait differences in control of different learning and memory systems will also be considered in which trait differences in learning and memory function are thought to potentially emerge from differences in level of prefrontal influence, differences in plasticity processes, differences in ascending neurotransmitter control, differential access to effector systems like motivational and motor systems. Finally, we present scenarios in which different mechanisms might interact. This review was conceived to become a jumping off point for new work directed at understanding these issues. The outcome of this work, in combination with other approaches, might improve understanding of the mechanisms of volition in human and nonhuman animals. © 2013 Wiley Periodicals, Inc.

KEY WORDS: hippocampus; amygdale; dorsal striatum; prefrontal cortex; ascending neurotransmitter systems; acetylcholine; systems interaction; competition

Department of Neuroscience, Canadian Centre for Behavioral Neuroscience, University of Lethbridge, Lethbridge, Alberta, Canada
Grant sponsor: Natural Sciences and Engineering Research Council of Canada.
*Correspondence to: Robert J. McDonald, Canadian Centre for Behavioral Neuroscience, Department of Neuroscience, University of Lethbridge, 4401 University Drive, Lethbridge, AB, Canada T1K 3M4.
E-mail: r.mcdonald@uleth.ca
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INTRODUCTION

Empirical and theoretical work suggest that the organization of memory in the mammalian brain and the neural systems that mediate them play a pivotal role in our thoughts, emotions, choices, actions, and even our personalities (McDonald et al., 2004; Everitt and Robbins, 2005; Robbins, 2005). According to this view, these brain systems, to a large extent, determine who we are and how we behave in particular situations. By logical extension, the neural systems mediating memory processes must have a pivotal role in both normal and abnormal manifestations of behavior. The theory guiding our research program is that memory function in the mammalian brain is organized into a group of neural systems mediating different memory functions and within this organization, normal thought and behavior arise from cooperative and competitive interactions between these different systems (White and McDonald, 2002). We and others have identified several of these neural systems involving hippocampus, rhinal cortex, amygdala, and dorsal striatum, as well as functional subsystems within these structures.

Abnormalities in the relationships between these systems and other parts of the brain are now thought to be responsible for a wide range of abnormal behavior and psychiatric disorders found in humans (White, 1996; Hanlon and Sutherland, 2000; Everitt et al., 2001; Hariri et al., 2002; Lipska and Weinberger, 2002; McEwen et al., 2002; McDonald et al., 2004). Accordingly, detailed information about the functions of these various brain systems, how and when they interact with each other, and the underlying neurobiological mechanisms supporting these functions is critical if we are to understand normal and abnormal manifestations of behavior in humans.

A subfield of systems neuroscience experimentation and theorizing attempts to reveal the functional specificities of each of these networks and more recently the nature of interactions amongst them. One fascinating issue that emerges from this work is how and under what circumstances does a specific learning and memory system guide behavior in a particular learning situation? This interacting memory systems approach

and related experimental research speaks directly to the issue of control of voluntary actions. We recently published a theory/review paper outlining the identity and organization of different learning and memory systems in the brain and how they might interact with each other and other neural circuits to control goal-directed behaviors (Gruber and McDonald, 2012). This paper was focused on potential neural mechanisms underlying these interactions and how one system gains control over another in a particular situation. These mechanisms focused on striatal outputs and dopamine as potential mechanisms for shifts in control by one neural circuit versus another.

This theoretical/review article is directed at understanding how external factors like task parameters and differences in internal neural mechanisms could account for trait differences in memory system function and control. These trait differences, in the context of learning and memory functions, would be controlled by the genetic make-up of the organism but also via environmental pressures the organism is exposed to during its lifetime. These individual differences in learning and memory function could affect which learning and memory system gains control of behavior in a given situation which could ultimately influence success/failure outcomes during their lifetime.

Various lines of evidence suggest that multiple mechanisms determine which system(s) gain behavioral control during an experience. These mechanisms include both external factors and internal neural mechanisms. The former includes external factors like the type of information to be learned and in which order this information is acquired, or the relative associative strength of each representation at any given stage of training. The latter includes executive decisions made by the prefrontal cortex based on information from various memory systems, availability of neurotransmitters (acetylcholine), and hierarchical organization of different memory systems with one dominating the others in the intact subject.

To understand how a learning and memory system might guide ongoing behavior in a particular situation, it is important to initially elaborate on two ideas. First, how do we define a learning and memory system in the mammalian brain. This is an important issue because one of the common criticisms of the multiple learning and memory systems view is that the whole brain is plastic and presumably the entire brain consists of innumerable learning and memory systems. We do not agree with this position because we do not equate plasticity with learning and memory nor do we think that all brain areas have the anatomical and representational complexity of the neural systems we are considering in our learning and memory system category. Nor do we believe that many neural systems in the brain have the combination of representational complexity and influence on a wide range of internal and overt behavioral responses. Clarity on this issue is a key to understanding the ideas presented in this theory paper. Second, the importance of understanding potential differences between classes of learning and memory tasks will be considered, and how these differences in tasks are a determinant of the nature of interaction between different learning and memory systems. Specifically, tasks in which different content can be acquired by different systems sequentially or simultaneously will be considered as they are thought to provide some of the best evidence for one system guiding behavior in a given behavioral situation (see McDonald and White, 1994).

MEMORY-BASED BEHAVIORAL SYSTEMS DEFINED

In a review/theory paper, White and McDonald (2004) provided a framework for trying to understand the organization of learning and memory functions in the mammalian brain. One element of the theory was to specify the elements that define a learning and memory system. According to this formulation, a learning and memory system has a central structure, but also includes the efferent and afferent connections of that central structure. In the case of the hippocampus, this would include areas like the sensory and association cortical regions, septum, nucleus accumbens, portions of the thalamus and hypothalamus, amygdala, and dorsomedial striatum (Fig. 1). The hippocampal system receives external and internally derived information (sensory, motor, motivational) and then processes it in its own style. This style is derived from the intrinsic organization of the system. For example, information that reaches the hippocampus is highly distributed throughout the structure as a result of an intrinsic neural architecture consisting of extensive vertical (trisynaptic circuit) and horizontal projections (association fibers). This unique processing style of the hippocampus allows for the formation of associative representations of disparate elements of information into a coherent memory representation of a place, context, or episode (Sutherland and Rudy, 1989; Gruber and McDonald, 2012). The central structure is thought to store some of this information under certain conditions (memory) in which the presence of elements of a particular situation exist in a specific relationship to one another producing a specific form of coherent neural activity. It is our view that each central structure is the permanent storage site for their unique form of memories, and this information is not transferred to cortical sites (Sutherland et al., 2010). Each system is capable of functioning independently of the other systems, but in normal circumstances they are thought to interact either synergistically or antagonistically to guide behavior.

Anatomical organization of two other learning and memory systems (dorsolateral striatum and amygdala) of interest for this article are also shown in Figures 2 and 3.

MEMORY-BASED BEHAVIORAL SYSTEMS: HIPPOCAMPUS, AMYGDALA, DORSAL STRIATUM

In this section, we will briefly describe the kinds of learning that occur in the three neural systems centered on the

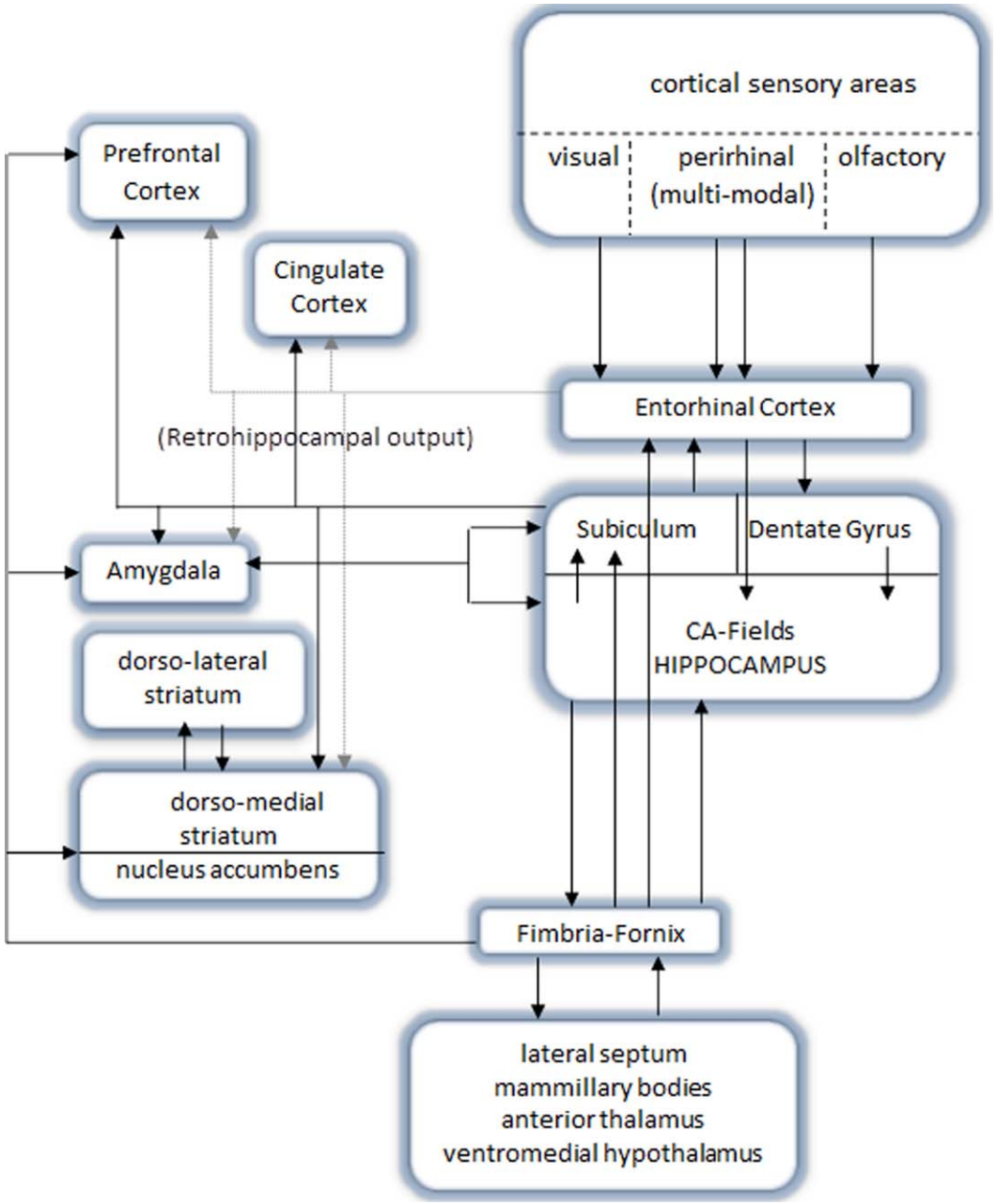

FIGURE 1. A simplified depiction of the major anatomical connections of the hippocampal learning and memory system (Adapted from White and McDonald, 2004). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hippocampus, amygdala, and dorsal striatum that have been implicated in learning and memory functions.

The hippocampal system (Fig. 1) is thought to be a learning and memory system that forms associative representations, consisting of disparate elements of information, into a coherent memory representation of a place, context, or episode (Sutherland and Rudy, 1989; Gruber and McDonald, 2012). This information is used to influence a variety of effector sites including those involved in postural, attention, autonomic, as well as voluntary motor control that can lead to specific patterns of motor responses (White and McDonald, 2002). The broad influence of the unique relational representation generated in the hippocampus on these different output systems can support different types of behavioral output including general approach/avoidance as well as specific reinforced motor responses and even complex navigational abilities (Gruber and McDonald, 2012) leading to successful goal-directed behavior. The functional effects of damaging the hippocampus are consistent with this view. A classic example of a task dependent on hippocampal processing is the spatial version of the water task

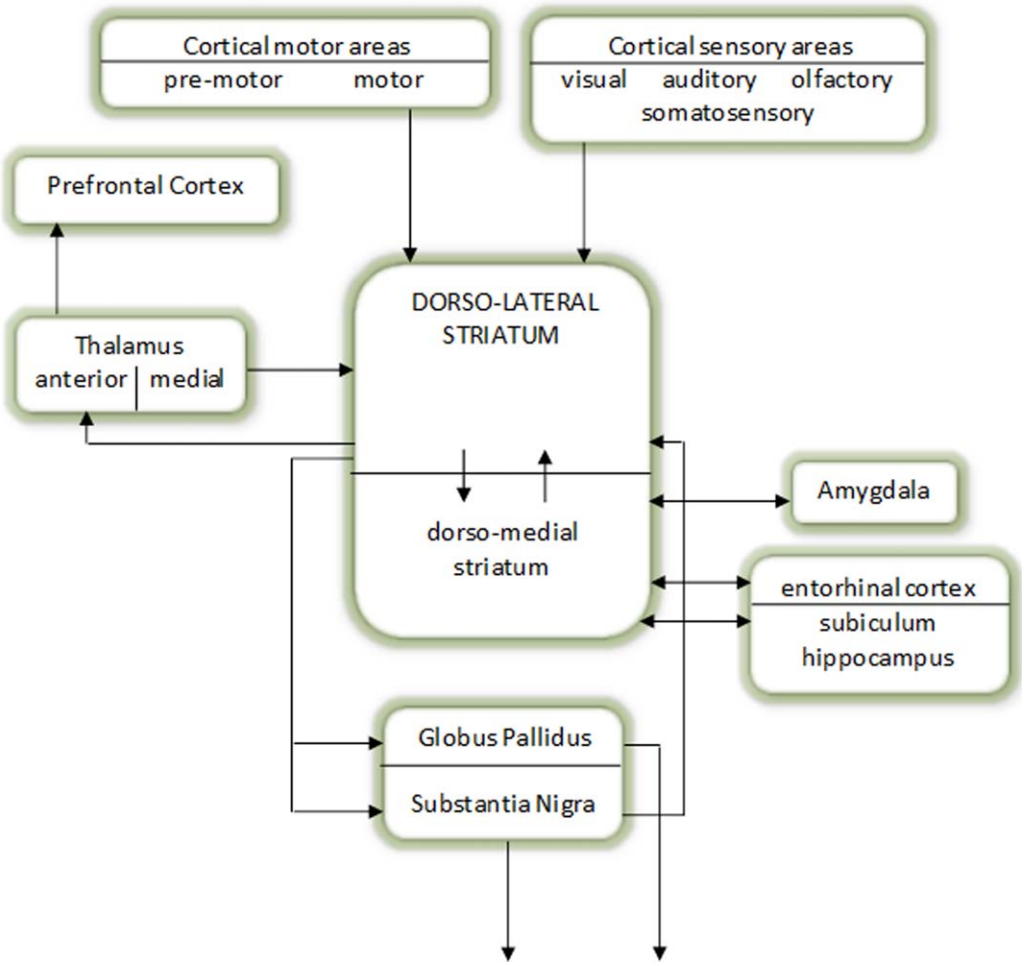

FIGURE 2. A simplified depiction of the major anatomical connections of the dorso-lateral learning and memory system (Adapted from White and McDonald, 2004). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(Morris et al., 1982; Sutherland et al., 1982). Briefly, rats are lowered into a circular pool of cool water and required to find a hidden platform location (goal). After only 5 days of training normal rats show impressive spatial navigational abilities and can exhibit direct swim paths to the platform from any randomly selected start positions (McDonald et al., 2004). Evidence suggests that rats remember the platform position and how to accurately navigate there by forming a representation of the features of the external environment or by forming a representation of the geometry of the pool, head direction information, and some allocentric details (polarizing cue). Rats with damage to the hippocampus are impaired at the acquisition and retention of this spatial navigational task (McDonald and Hong, 2000).

The amygdala-system (Fig. 2) is thought to acquire and store associations of neutral cues and co-occurring biologically significant events (positive or negative). This form of classical conditioning is achieved via the unique anatomy of the amygdala in which there is a convergence of sensory information from all modalities combined with information about positive (reward) and negative (fear) valence. The amygdala is thought to form these associations so that presentation of the predictive cue alone can elicit approach or avoidance depending on the valence of the biologically significant stimulus linked to it (White and McDonald, 2002).

This is achieved via the ability of amygdala neurons to reactivate the brain stem, hypothalamic, and basal forebrain areas that elicit the reward or fear state (Kapp et al., 1990; White and McDonald, 2002). These associations allow the animal to predict important events and to modify their behavior accordingly. The functional effects of damage to the amygdala are consistent with this view. A classic example of a learning and memory task dependent on the amygdala is an aversive classical conditioning task in which a discrete cue is associated with the onset of an aversive experience (paraorbital shock). Kapp et al. showed that rats with damage to the central amygdala were unable to learn that the neutral cue was associated with the occurrence of the shock (Kapp et al., 1979).

The dorso-lateral striatum system (Fig. 3) has been implicated in stimulus-response habit learning (Packard et al., 1989;

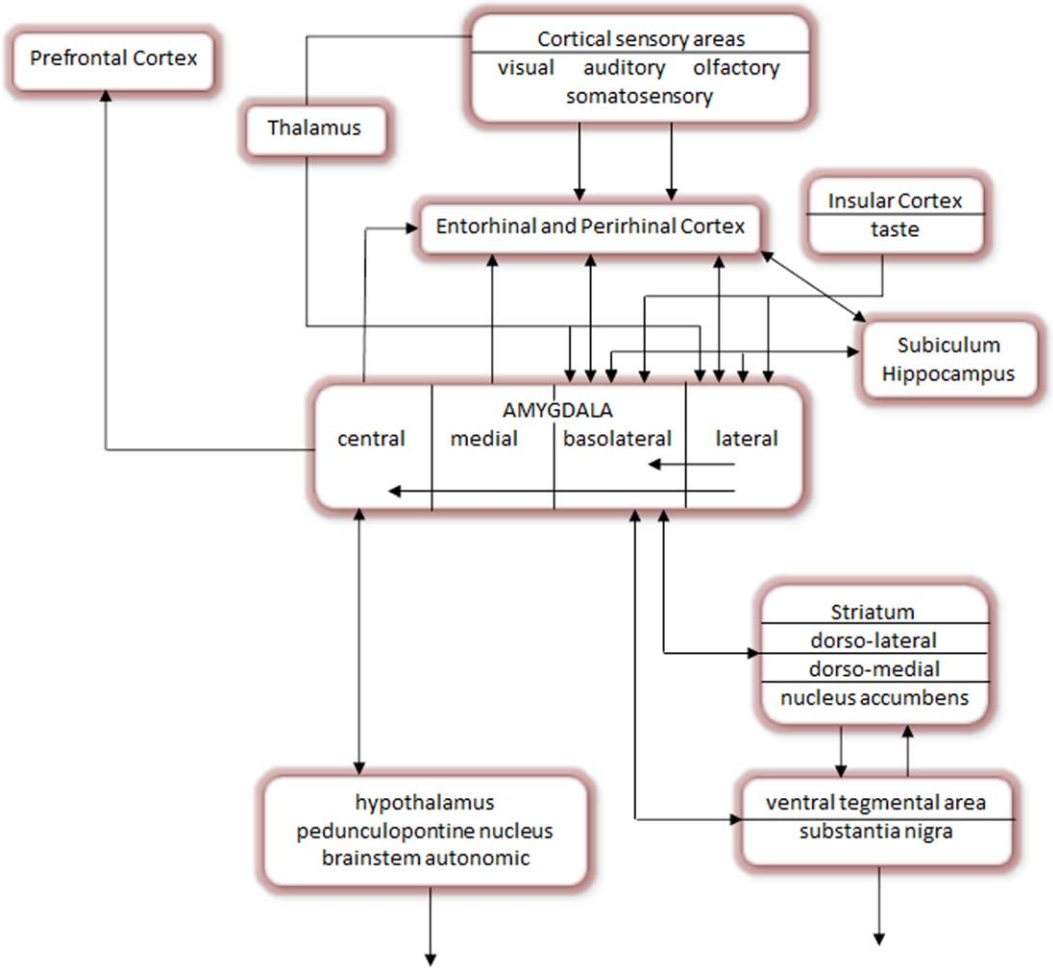

FIGURE 3. A simplified depiction of the major anatomical connections of the amygdala learning and memory system (Adapted from White and McDonald, 2004). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Reading et al., 1991). The information acquired during this type of instrumental learning experience is an association of a stimulus with a specific instrumental response that leads to reinforcement. After repeated reinforced stimulus-response pairings the stimulus triggers a response in an automatic, habitual-like manner. For this type of learning, the specific motor response is part of the representation. The anatomy of the dorsolateral striatum could support this type of learning because it receives information about the sensory environment and from the motor system (McGeorge and Faull, 1989). These instrumental associations can lead to conditioned responses in which the reinforced cue elicits the associated response via output to higher order motor areas including the globus pallidus and substantia nigra (Gerfen, 1985). A good example of an instrumental task dependent on the dorso-lateral striatum is a conditional discrimination task developed for operant chambers. For this task, rats are trained to press a lever when a light is present and pull a chain when a tone is present to obtain palatable food reward. Normal rats acquire this conditional discrimination, but rats with neurotoxic lesions of the dorsolateral striatum show severe impairments on the acquisition and retention of this instrumental task (Featherstone and McDonald, 2004; Featherstone and McDonald, 2005). This is an interesting example because the rat must learn to make a specific motor response when a particular cue is present to obtain maximal rewards.

TASK ANALYSIS

On the surface, it seems obvious to a human observer what kinds of information a rodent acquires during acquisition of a specific learning and memory task. For example, multiple experiences with a neutral cue (tone) that predicts the presence of an aversive cue (foot-shock) results in the encoding of memories of the tone + shock association, probably using classical conditioning processes and recruitment of relevant brain areas like the amygdala (Bagshaw and Benzies, 1968; Kapp et al.,

1979). Interestingly, under these training conditions rats also learn about the context chamber in which these events occur (Fanselow, 1990) and that the larger testing room (Antoniadis and McDonald, 1999) predicts the occurrence of the shock as well. These different representations acquired during this simple conditioning procedure appear to be acquired and stored in different learning and memory systems (Antoniadis and McDonald, 2000). This example illustrates the complexity of memory formation even on a task that would be described as a simple classical conditioning task based on behavioral observation alone.

The complexity of neural representations acquired during learning inspired McDonald and White (1993) to complete a task analysis based on the interacting memory systems idea in which they argued that there are at least three different types of tasks that require different types of dynamic interactions between memory systems. Type A tasks require a single system and the other systems either interfere or have no influence (McDonald and White, 1993). When a system interferes with acquisition, this influence is sometimes referred to as a competitive interaction. An example of a Type A task is the standard, spatial version of the water task. The task requires the animal to using allocentric information outside of a circular pool to locate a hidden platform location. Acquisition and retention of this task requires the hippocampus (Sutherland et al., 1982), but not other learning and memory systems including the dorso-lateral striatum (Packard and McGaugh, 1992) or the amygdala (Sutherland and McDonald, 1990).

Type B tasks can be acquired by multiple systems, in parallel, with each system capable of supporting learned behavior (McDonald and White, 1993; 1994; 1995). A good example of a Type B task is the cue/place version of the water task (McDonald and White, 1994). For this task, an escape platform can be found using both a visible beacon and the absolute spatial location as defined by allocentric cues in the testing room. Evidence suggests that hippocampus acquires information about the spatial location of the platform, while the dorso-lateral striatum acquires information about responses directed at the visible platform. This is an example of tasks for which the unique representations acquired in more than one system result in the same behavior, in this case escape from cold water.

Type C tasks utilize the functions of two or more systems for an accurate solution and performance (Phillips and LeDoux, 1992; Ferbinteanu and McDonald, 2001). An example of a Type C task is fear conditioning to context in which the hippocampus is thought to form a complex representation of the various stimulus elements that define that specific context and the amygdala provides this representation with access to certain unconditioned fear circuits (Antoniadis and McDonald, 2002).

The neural computations and dynamic interactions between memory systems necessary to acquire these tasks (Type B and C) are thought to be based on synergistic or cooperative interactions and information about how different memory systems might gain behavioral control has been obtained almost exclusively from experiments using these types of tasks.

EXTERNAL INFLUENCES ON WHICH NEURAL SYSTEM CONTROLS BEHAVIOR

One set of factors that are hypothesized to influence which learning and memory system controls behavior are external to the subject and related to the nature of their learning experience and specific task features. These factors include what order different types of information are learned and the amount of training.

The "Who Came First" Control Mechanism

The "who came first" mechanism, for how a specific learning and memory system might gain control of behavior, proposes that because some learning and memory tasks employ different stages of training, the first system to acquire information gains control of behavior. These kinds of designs might create a situation in which one learning and memory system might acquire information during an initial stage of training and then another system is required for a subsequent component of training. What can happen in these training situations is that the first system may gain control over a common output node and then prevent or hinder access by another system.

This kind of situation was demonstrated in a series of experiments using a conditioned place preference task (CPP). The CPP task is an appetitive classical conditioning paradigm that uses distal spatial cues, like those used in place navigation tasks, as the conditioned stimuli. Normal rats show a conditioned place preference after four but not after two training trials (Fig. 4). The acquisition of this task seems to require both the amygdala- and hippocampal-based learning and memory systems (McDonald and White, 1993; 1995) with the dorsal hippocampus providing complex spatial information and the amygdala providing access to reward information (Ferbinteanu and McDonald, 2001). Interestingly, rats with ventral hippocampal lesions or fornix lesions show enhanced acquisition on the CPP task suggesting that the ventral hippocampal circuit actively inhibits the amygdala-based learning and memory system. Figure 5 shows that rats with ventral hippocampal or fornix lesions required fewer training trials (two training trials) to show a CPP, and rats with amygdala damage were unable to show a CPP even following four training trials.

It appears that the ventral hippocampal effect is not a general inhibition effect but was based on information acquired by the hippocampus during habituation procedures in which the subjects were allowed to explore the entire maze apparatus for two, 10 min epochs. Evidence for this claim comes from an experiment showing that normal rats given habituation procedures on a radial maze in a different context show enhanced CPP learning similar to that shown by rats with hippocampal damage given pre-exposure and training in the same context (Fig. 6) (White and McDonald, 1993). The idea is that the ventral hippocampus acquired contextual information during the pre-exposure to the training room that subsequently interfered with the amygdala's ability to gain control over behavior,

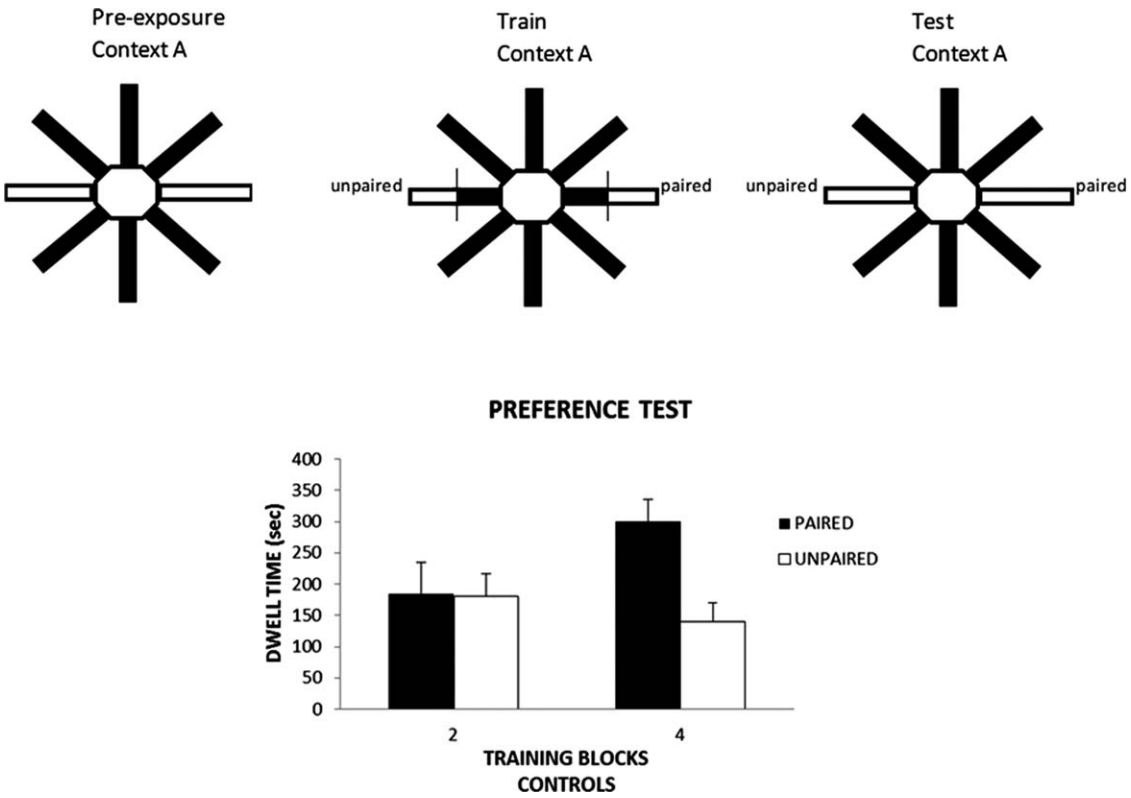

FIGURE 4. (Top Panel) An illustration of the training method employed for the standard version of the conditioned place preference (CPP) developed for the radial maze. Pre-exposure, training, and testing all occurred in the same context. Pre-exposure: During this phase, a rat was given free access to the central position and the to-be trained arm locations for 10 min. Training: For training, a rat was placed at the end of the paired arm location and given a large amount of a palatable food for 30 min. On the following day, the rat was placed in the unpaired location and no food was present for 30 min. The rat was not allowed to move around the arm locations or central location during training. Testing: On the test day, the rat was given free access to the central position and the two arm locations. (Bottom Panel) The results from the preference test following two (4 days) or four training trials (8 days) in control rats. Under these training conditions, four training trials were required for the control rats to show a preference.

requiring more Pavlovian training sessions before showing a CPP (McDonald and White, 1993; 1995). Our recent work showing that the ventral hippocampus is essential for learning what events predict non-reinforcement is consistent with this view (McDonald and Hong, 2006).

One explanation of this effect is that the amygdala and ventral hippocampus compete for behavioral control at the level of the medial nucleus accumbens. Hippocampal activity and encoding processes during the pre-exposure phase of the CPP task could elicit neuronal changes in the medial nucleus accumbens that could inhibit amygdala access to the same neuronal site leading to hindering of amygdala control over behavior (Ferbinteanu and McDonald, 2001).

There is also electrophysiological data that is consistent with the claim that hippocampal activation of medial nucleus accumbens inhibits the ability of the amygdala to influence this same site (Mulder et al., 1998) and elegant work showing that the nucleus accumbens acts as a "switchboard" for goal-directed behaviors by dynamically switching from hippocampal to other representational influences (Gruber et al., 2009; Gruber et al., 2009).

Another possible mechanism that impairs the amygdala's ability to guide behavior during CPP training is that the initial ventral hippocampal influence on the nucleus accumbens might reduce a dopamine-mediated "reward signal" there that normally reaches the amygdala as a neural representation of the unconditioned stimulus or primary reward. Primary rewards like water, food, and sexual partners are thought to produce drive reduction, and theorists (Wise, 1980) argue that obtaining rewards results in activation of dopamine neurons in the mesolimbic dopamine areas which terminate in areas like the nucleus accumbens. If this dopamine-mediated primary reward signal is reduced via this mechanism, it could lead to retarded stimulus-reward learning. This mechanism would be described as a "US reduction" mechanism that leads to impaired learning in one memory system by the action of another system. Consistent with this idea, there is evidence showing that the ventral hippocampus can modulate dopamine release in the nucleus accumbens. Experiments using microdialysis have shown that electrical stimulation of the ventral hippocampus elevates dopamine release in areas like the nucleus accumbens (Taepvarapruk et al., 2008), and neuroanatomical evidence shows that the

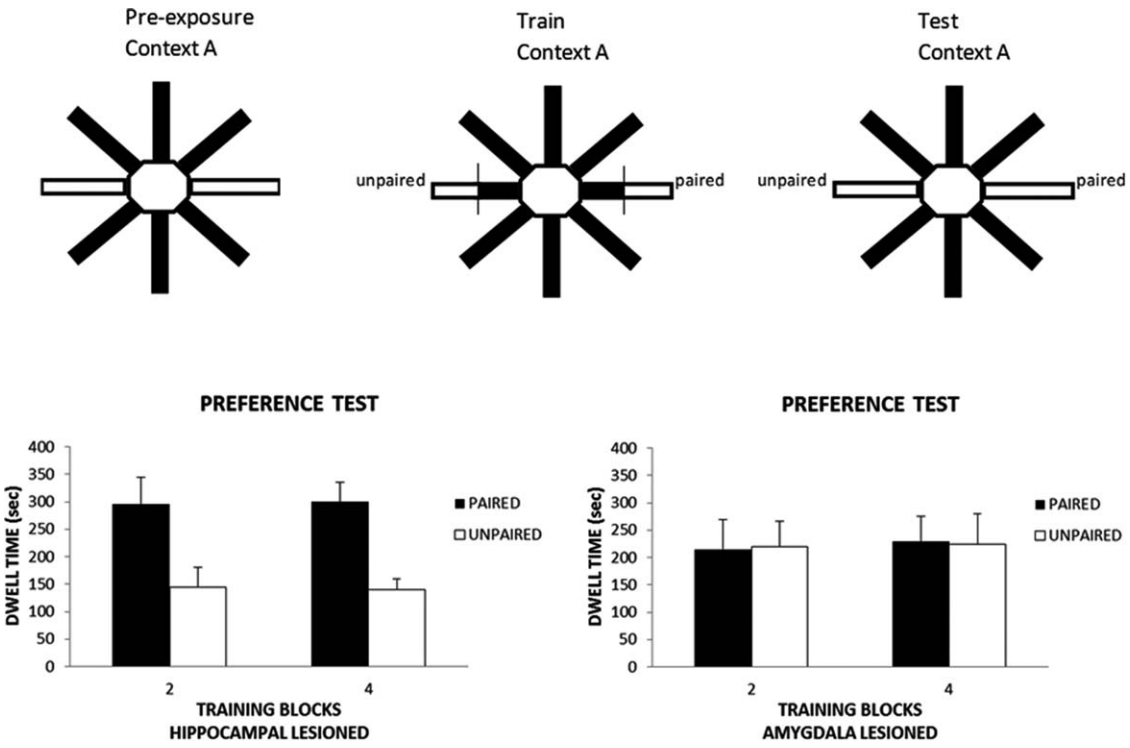

FIGURE 5. (Top Panel) The same paradigm described in Figure 4 was used to assess the effects of damage to the hippocampus or amygdala on this learning task. (Bottom left panel) Rats with hippocampal damage showed a CPP even after two training trials, an amount of conditioning that was not sufficient to produce a CPP in normal rats. (Bottom Right Panel) Rats with amygdala lesions were impaired at acquiring the CPP regardless of the amount of training. This pattern of data suggested that an intact amygdala is necessary to show this kind of classical conditioning and that the hippocampus somehow interfered with this kind of learning. This interference was thought to occur via a representation (spatial) that was acquired by the hippocampus during preexposure.

ventral hippocampus projects to the nucleus accumbens (Groenewegen et al., 1987).

The hippocampal-amygdala interaction described above is in contrast to many examples of Pavlovian conditioning driving instrumental responding to the same goal (Rescorla and Solomon, 1967). These tasks would fit into the Type C category described in the previous section on learning and memory task analysis. One example of this kind of effect is a learning phenomenon sometimes referred to as the Pavlovian-to instrumental transfer (PIT) effect (Estes, 1943; Lovibond, 1983). During one version of PIT training, subjects are given instrumental training in which responding on one bar results in one outcome and responding on another bar results in a different outcome. Following this training, the same subjects are given Pavlovian conditioning in which those same outcomes are associated with different conditional stimuli (tone and light). During a transfer test, the conditioned stimuli are presented and the subjects are allowed to respond on the levers. In these experiments, the Pavolvian cue enhances responding in the instrumental task in an outcome specific manner. For example, various experiments have shown examples of PIT in which an amygdala-based Pavlovian association supports acquisition and maintenance of an arbitrarily reinforced instrumental response (Corbit and Balleine, 2003; Holland and Gallagher, 2003; Zorawski and Killcross, 2003).

In summary, it seems clear from these two examples that initial learning by one neural system can have fundamentally different effects on subsequent learning by another system. During CPP training information acquired by the hippocampus during habituation procedures inhibited the influence of information acquired by the basolateral amygdala during subsequent Pavlovian training procedures. It was hypothesized that the hippocampus hinders the amygdala's influence on behavior by limiting access to an output node, the nucleus accumbens. In contrast, information acquired by the amygdala during Pavlovian training procedures subsequently enhances acquisition or maintenance of an operant task using the same outcomes. One obvious difference between these demonstrations is that in the former the information acquired by the hippocampus may be in conflict with the information acquired by the amygdala, thus causing the interference effect, whereas in the latter case, the information acquired by the amygdala is complementary to the information that will be acquired by the neural systems necessary for the operant portion of the task, presumably the dorsolateral striatum.

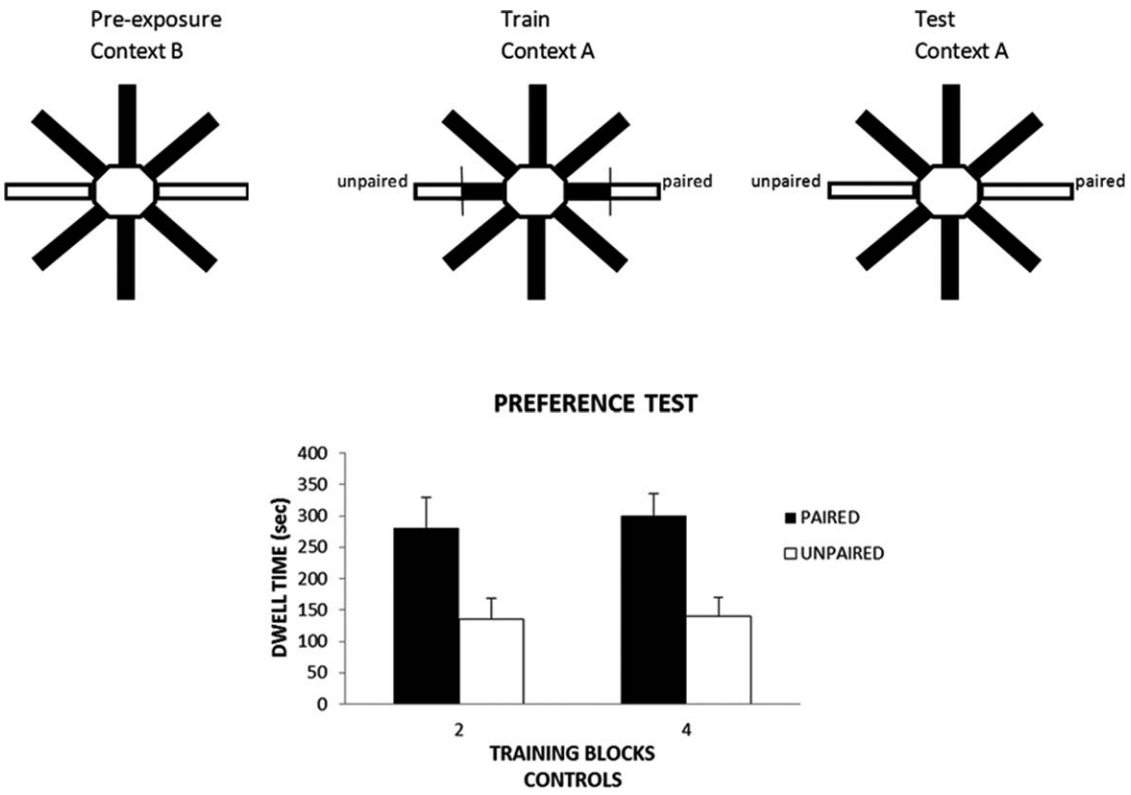

FIGURE 6. (Top Panel) A variant of the standard version of the CPP described in Figure 4. The only difference is that the pre-exposure phase occurs in a different context than training and testing. (Bottom Panel) The results from the preference test following two (4 days) or four training trials (8 days) in control rats. Under these training conditions, two training trials were required for the control rats to show a preference. It was concluded from this pattern of data that information acquired during pre-exposure in the same context as training inhibited or interfered with learning during training.

Associative Strength Control Mechanism

Recent work, using a variety of type B tasks, has shown that the DLS has little influence early in training but as training continues into the middle and late stages, this system exerts a strong influence on behavior. An important example of this kind of demonstration comes from experiments using a plus-maze which was inspired by early animal learning studies of Tolman and Restle.

Tolman (Tolman et al., 1946; Restle, 1957) showed that when rats are trained to respond to a specific location on a plus-maze from the same start position to obtain food, they will use a place strategy early in training and then switch to a S-R strategy later in training. Packard et al. replicated this finding and showed that the hippocampus controlled the animal's performance on the task early on and then the dorsolateral striatum exerted control in the later stages of training (Packard and McGaugh, 1996; Packard, 1999). This pattern of data suggests that during training on tasks that have both hippocampal and dorsal striatum-based solutions, the hippocampus gains control early during training and then with many training repetitions the dorsolateral striatum takes over. Because this is an amount of training transition effect, it suggests that under these conditions the mechanism by which the dorsolateral striatum gains control over behavior is by reaching a threshold level of associative strength. This associative strength is enough to end hippocampal control over behavior. This pattern of data also suggests the possibility that the hippocampus reaches asymptotic associative strength levels faster than the dorsolateral striatum system. Consistent with this idea is evidence suggesting that, in certain training circumstances like place or context learning, the hippocampus acquires information, at a functional and neurophysiological level in relatively few trials and likely reaches asymptotic levels of associative strength after a sparse amount of training (Muller et al., 1987; Rudy et al., 2004; Stote and Fanselow, 2004). Furthermore, it is now being argued that the hippocampus, during contextual fear conditioning, actually inhibits other nonoptimal learning and memory systems during training. This view would account for recent demonstrations that lesions of the hippocampus impair nondiscriminative fear conditioning to context in the retrograde direction but not in the anterograde direction (Lehmann et al., 2007). Interestingly, this effect disappears if sufficient amounts of training occur, presumably allowing non-hippocampal learning and memory systems like the amygdala to acquire sufficient associative strength to control appropriate behavioral responding (Lehmann et al., 2009).

Taken together, this work suggests that different learning and memory systems have different learning rate parameters and asymptotic associative strength might be one determinant by which one system gains control over behavior. Interestingly, although associative strength is determined to some extent by the amount of training, this external factor only manifests itself because each learning and memory system might have a unique learning rate parameter. A learning rate parameter just refers to the features of the neurobiological learning mechanism which determine the shape of the learning curve and how long it takes the learning mechanism in that system to reach asymptotic levels of performance. The learning rate parameter is most likely innately determined and would be considered an intrinsic neural mechanism that interacts with external training parameters to determine associative strength and presumably behavioral control by one system over another.

INTRINSIC NEURAL MECHANISMS INFLUENCING WHICH SYSTEM CONTROLS BEHAVIOR

Another set of factors that are hypothesized to determine which learning and memory system controls behavior in a given situation are various mechanisms found in the brain of the subject (internal neural mechanisms). Our previous theory paper (Gruber and McDonald, 2012) focused on striatal outputs and dopamine as neural mechanisms of memory system control. This article will focus on executive decisions made by the prefrontal cortex, ascending neurotransmitter systems acting as a switching mechanism of control, and a neural organization found in the mammal in which one memory system dominates the others in most situations.

Prefrontal Cortex as Decision Maker

The medial prefrontal cortex is likely to play a significant role in determining which learning and memory system gains control over behavior in a particular situation, and this would be consistent with the idea that the medial prefrontal cortex is critical for a range of executive processes including decision-making (Kolb, 1984; Moscovitch, 1992; Wise, 1996; Duncan and Owen, 2000; Chudasama and Robbins, 2006; Rich and Shapiro, 2009). The prefrontal cortex receives information from most identified learning and memory systems as well as areas implicated in motivational states and attentional processes and influences areas thought to modulate motor output like the nucleus accumbens and DMS (Kolb, 1984; Reep, 1984; Groenewegen et al., 1990) as well as via projections to the motor cortex. Our view is that the prefrontal cortex influences actions after integrating the subject's current motivational state, the current situational context, and any information provided from different learning and memory systems. This structure integrates this information and influences decision about which learning and memory system and associated neural circuits will gain control over behavior at that moment (McDonald et al., 2007a; McDonald et al., 2008a).

There are different types of empirical evidence in the literature consistent with this view. For example, rats with medial prefrontal cortex damage are impaired at behavioral flexibility when switching from a hippocampal-based place learning response to a dorsolateral striatum-based egocentric response and vice versa (de Bruin et al., 1997; Ragozzino et al., 1999) as well as switching from one place representation to another in the water task (Gemmell and O'Mara, 1999; McDonald et al., 2008a). Inactivations of infralimbic portions of the medial prefrontal cortex seem to switch rats from habitual responding back to goal-directed responding (Coutureau and Killcross, 2003), suggesting this structure plays some fundamental role in response performance. Interestingly, inactivations of the prelimbic area seems to drive a subject to habitual responding without first learning goal-directed behaviors (Killcross and Coutureau, 2003). We have also shown that the medial prefrontal cortex lesions that include damage to the prelimbic and infralimbic areas maintains the behavioral influence of a ventral hippocampus mediated context-specific inhibitory association (McDonald et al., 2007a) instead of allowing a stimulus-response association to gain control of behavior.

Evidence also suggests that portions of the orbital frontal cortex are involved in enabling particular learning and memory systems to gain behavioral control in specific situations (Roberts et al., 2007; Schoenbaum et al., 2007; Tait and Brown, 2007). It is thought that orbital frontal cortex does this by integrating information about rewards and punishments and their predictors via access to representations in brain areas like amygdala and hippocampus.

It seems likely that different portions of the prefrontal cortex are involved in determining which learning and memory system gains control over behavior. This has often been thought to be the only mechanism by which behavioral decisions are made. However, the current analysis will provide evidence and analysis suggesting that there are non-prefrontal cortex mediated mechanisms by which a learning and memory system can obtain control and future work will reveal under what conditions these mechanisms are activated and whether they work in concert in some situations. It seems likely that some of the non-prefrontal mechanisms can work without prefrontal cortical involvement in some instances and not others. For example, during reversal learning it is difficult for mechanisms like the associative strength mechanism to influence behavior quickly enough without prefrontal intervention because it likely takes a significant amount of time to breakdown a previous association and build up a new one.

Modulatory Neurotransmitter System Activation As a Switching Mechanism

Other research suggests that modulatory neurotransmitter systems enable the transition from hippocampal to dorsolateral striatum control. This work utilized the cross maze in which rats are trained, for example, to go from the south arm to the

east arm for a reward. This task can be solved using either a response strategy or a place strategy. Normal rats tend to use a place strategy early in training and switch to a response strategy late in training and the hippocampus is involved in the early learning and the dorsolateral striatum is involved in the late emerging response learning (Packard and McGaugh, 1996). Chang and Gold (2003) used this task and measured acetylcholine levels simultaneously in the hippocampus and dorsolateral striatum during all phases of training. The results showed elevated acetylcholine levels in the hippocampus early in training and these levels were maintained throughout. The acetylcholine levels in the dorsolateral striatum increased over training reaching 40% higher amounts from the beginning of training. These increases in the dorsolateral striatum at the later stages of training are around the time in which this neural system starts gaining control over behavior (Packard and McGaugh, 1996). One interpretation of these effects is that the increases in acetylcholine release in the striatum are the mechanisms by which the dorsolateral striatum wrestles control from the hippocampus on tasks that have multiple solutions (type B tasks), and this mechanism might also be how the hippocampus tries to maintain control.

A similar effect has been reported for the dorsomedial striatum during place reversal learning and it has been argued, based on this kind of data, that the actions of the ascending cholinergic system in this brain area is to enable shifting behavioral patterns during changing conditions (Ragozzino and Choi, 2004). Based on neural connectivity and the effects of damage to the dorsomedial striatum, it seems likely that this effect is mediated in concert with prefrontal cortical executive functions.

This work suggests that activation of ascending neurotransmitter systems, like the cholinergic system, might be one mechanism by which one learning and memory system gains control over behavior in a given situation.

Activation of these systems might provide a neurochemical threshold that causes a switch from one learning and memory system to another or might modulate associative strength in one system over another. It is highly likely that other ascending neurotransmitter systems have similar effects on these processes. Interestingly, recent work has shown that the internal state of the animal can influence which learning and memory system gains control in a freely behaving situation (Elliot and Packard, 2008), and these effects might be related to the activation of modulatory neurotransmitter influence on memory system control.

Hippocampus As the Default Learning and Memory System

The multiple learning and memory systems view of the organization of learning and memory in the mammalian brain suggest that different systems can acquire and store information in parallel and relatively independently. According to this view the anterograde and retrograde effects of lesions to a particular experiment should be the same. For example, rats with hippocampal lesions are impaired on the acquisition of the spatial version of the Morris water task and show dramatic retrograde memory impairments on the same task (Morris et al., 1982; Sutherland et al., 1982; Sutherland et al., 1983).

A recently formulated alternative view suggests that the hippocampus is always required for the storage and retrieval of some types of information acquired during learning, including relational but also some types of nonrelational memories that are not dependent on the hippocampus in the anterograde direction (Sutherland et al., 2001).

One set of experiments showing this pattern of effects used a visual water task (see Prusky et al., 2000) to train rats on picture discriminations. The visual water task was composed of a trapezoidal shaped metal pool of water with a hidden platform located at one end of the pool. The end wall of the tank is transparent. On one side of the trapezoid was a long barrier above water level, dividing the end in half to create two arms for the rat to swim into. On each side of the barrier, displayed through the transparent wall, were two flat CRT computer monitors showing a black and white picture, one rewarded stimulus and one unrewarded stimulus. Each picture stimulus displayed on the monitors had a near equal amount of luminance. The picture discrimination task required rats to swim to a hidden platform that was submerged in front of the monitors that displayed the rewarded (+) picture. At the beginning of each trial, the rat was released into the pool at the wall opposite to the pictures stimuli and allowed to swim to one of the stimuli. If the rat swam to the rewarded picture, the rat reached the hidden platform to escape the water and was returned to its holding cage. If the rat swam to the incorrect picture, then the rat remained in the pool until it found the platform.

Acquisition of this visual discrimination task was not impaired in rats with hippocampal lesions, but these subjects were impaired in the retention of picture information acquired during a conditional portion of the task that does not require the hippocampus in the anterograde direction (Driscoll et al., 2005).

Rats with hippocampal lesions also show retention deficits on a cued fear potentiated startle paradigm (Lehmann et al., 2009) and certain types of object recognition tasks (Lehmann et al., 2006; Lehmann et al., 2007) that do not require the hippocampus in the anterograde direction. This and other work has led these researchers to the conclusion that if the hippocampus is present during learning it actually occludes learning in other systems.

One issue surrounding this view and these kinds of demonstrations is what the nature of the retention deficit is, and the underlying cause (McDonald et al., 2007b). The occlusion of learning in other systems by an intact hippocampus is one mechanism to explain these effects but other explanations for these kinds of retrograde hippocampal deficits are possible, including: (1) different systems compete for behavioral control at some output node; (2) parallel learning by two or more systems but the hippocampus gains associative strength faster; (3) if the hippocampus is present during learning, it alters the

neural representation in other systems making it difficult for memory retrieval if the hippocampus is absent following training; (4) secondary effects of the lesion disrupt performance; (5) the hippocampus acquires incidental information that is not necessary for acquisition but if missing during retention can affect performance. A brief explanation of these potential mechanisms for retrograde memory impairments following hippocampal lesions on tasks that do not require the hippocampus in the anterograde direction can be found below.

There is good evidence that the hippocampus, if present during learning, acquires information in parallel with other learning and memory systems like the dorsolateral striatum and amygdala (Packard et al., 1989; McDonald and White, 1993; 1994; 1995; White and McDonald, 1993; Ferbinteanu and McDonald, 2001; Featherstone and McDonald, 2004a; 2004b; 2005a; 2005b; McDonald et al., 2002; McDonald et al., 2004; McDonald and Hong, 2004; McDonald et al., 2006; McDonald et al., 2007b; McDonald et al., 2008b) and in some cases these systems compete for behavioral control. For example, we have shown that if the hippocampus is present during the habituation phase of the CPP task, it inhibits the ability of the amygdala to gain control over behavior following Pavlovian conditioning procedures. Evidence was presented in these experiments suggesting that the learning was not occluded in the amygdala but access to an output node was actively restricted by the hippocampus.

A different idea to explain these kinds of effects is that the hippocampus may have a fast learning rate parameter that allows it, in certain situations, to acquire a solution quicker than other systems. For example, recent work has shown that if only a single session of fear conditioning to context training is given then the hippocampal system dominates (Lehmann et al., 2009). However, with multiple learning sessions enough information can be captured by a non-hippocampal system, like the amygdala, to support a contextual fear memory that will survive complete damage to the hippocampus even in the retrograde direction. This pattern of results suggest that the hippocampus dominates in minimal training situations because it has a faster learning rate parameter and, therefore, removal of this structure would result in retrograde memory impairments.

Another possible explanation for these kinds of paradoxical anterograde/retrograde effects is that removal of the hippocampus, after learning, results in a retrieval deficit. The idea here is that if the hippocampus is present during task acquisition, it could alter the nature of the representation formed in some of the other systems. In other words, if the hippocampus is damaged post-training, it might be difficult for the other system to retrieve the learned information. A potential example of this kind of effect was recently reported (Featherstone and McDonald, 2005b) using an operant simple discrimination task. Rats were pretrained to make a voluntary forelimb movement (barpress or chain pull) during a specific cue presentation (tone or light). After reaching asymptotic performance levels on this version of a go/no go task, the subjects were given neurotoxic lesions of the dorsolateral or dorsomedial striatum. Following a recovery period, the subjects were retrained and the results showed that rats with dorsolateral striatum damage were impaired in retention and re-acquisition of the task, a result that is consistent with the effects of the same lesions in the anterograde direction. Rats with dorsomedial striatum damage also showed impairments in retention and re-acquisition of the task, a result that was inconsistent with the effects of dorsomedial striatum lesions in the anterograde direction (Featherstone and McDonald, 2005b). The different anterograde versus retrograde memory impairments exhibited by rats with dorsomedial striatum damage is interesting because of the important anatomical and functional relationship between this neural structure and the hippocampus (McGeorge and Faull, 1989; Devan and White, 1999). It is possible that this specific retrograde amnesia effect following dorsomedial striatum damage occurred because the hippocampus became part of a circuit of synaptic plasticity mediating the learned behavior that included the dorsomedial striatum even though neither structure was necessary. In this situation, these neural structures become part of the retrieval process leading to accurate recall of the memories mediating the learned behavior. If the hippocampus is removed before acquisition then the dorsomedial striatum is not engaged in a plasticity circuit, and this retrieval problem would not occur because the other parts of the circuit are the same as during original training, currently available and can be activated.

The paradoxical anterograde/retrograde effects of hippocampal damage could also be explained by the fact that these kinds of lesions could also produce secondary effects on behavior, unrelated to learning and memory that could disrupt performance. For example, these effects could include over-activity effects following these types of lesions (McDonald and White, 1993; Wilkinson et al., 1993), particularly if the subjects are food deprived or stressed. Over-activity could lead to performance deficits that are not necessarily due to learning and memory impairments and these effects might be more pronounced immediately following the lesion.

Finally, our recent demonstration that the hippocampus can incidentally acquire information during acquisition of a simple discrimination task might be one explanation why some laboratories report retrograde memory loss following hippocampal damage on tasks not sensitive to hippocampal damage in the anterograde direction (McDonald et al., 2002; McDonald et al., 2006; McDonald et al., 2007b). The idea is if a brain area encodes information that is necessary for acquisition of the task, lesions of that area will result in deficits in learning. However, a brain area may also encode information that is not necessary for acquisition of the task (such as contextual information and stimulus-reward associations). Since such information is not necessary for learning of the task, lesions of an incidental memory system would have little impact on subsequent acquisition of a task in a naive animal. However, given that the representation formed during acquisition in the intact animal is likely a combination of both necessary and incidental learning, postacquisition removal of an incidental memory system could greatly alter the representation that the animal is relying upon to perform the task, and could be sufficient to disrupt performance.

Regardless of the mechanism, the finding that there are different effects of anterograde versus retrograde lesions to the hippocampus on certain learning and memory tasks (Sutherland et al., 2001) should prove to be a fascinating and fruitful line of novel enquiry that will promote new levels of understanding of this complex brain system and its influence on other learning and memory systems and voluntary behavior.

EXTERNAL FACTORS INFLUENCING WHICH MEMORY SYSTEM CONTROLS BEHAVIOR: AN EXAMPLE

In this section, we will provide an experimental example illustrating how external factors like task parameters can influence which system controls behavior during learning using our conceptual model for these systems interactions and a simple instrumental task (Gruber and McDonald, 2012). In this model, a ventral emotional memory network involving ventral striatum, amygdala, ventral hippocampus, and ventromedial prefrontal cortex selects behavioral responding to stimuli according to their associated affective outcomes. This system engages autonomic and postural responding (avoiding, ignoring, and approaching) in accordance with associated stimulus valence (negative, neutral, and positive), but does not engage specific motor responses. Rather, this emotional system suppresses or invigorates actions that are selected through competition between cognitive control involving dorsomedial striatum and habitual control involving dorsolateral striatum. The hippocampus provides contextual specificity to the emotional system, and provides an information rich input to the goal-directed system for navigation and discriminations involving ambiguous contexts and complex sensory configurations.

Using this conceptual model, let's look at what the effects of different training parameters and internal neural mechanisms might have on whether a particular learning and memory system would gain access to behavior. For this thought experiment, the instrumental task occurs in an operant chamber in which the rat is reinforced with palatable food pellets for pressing a lever when a light is present and for pulling a chain when a tone is present. Early in training, the emotional system and associated circuits (amygdala, hippocampus, and nucleus accumbens) would engage and motivate the animal to approach and maintain contact with the food hopper, lever, and the chain. The rat would also learn with this system to attend to the light and tone and to use these as signals for the presence of a reward. Further on in training, the dorsomedial striatal system would be engaged allowing the animal to press the lever in the presence of the light and pull the chain only in the presence of the tone. This goal-directed learning and memory system would elicit general motor responses leading to improved discrimination scores. Late in training, after many reinforced trials the dorsolateral striatal habit system would be engaged and would obtain control over behavior providing precise motor responses during the appropriate cue presentations leading to almost robot-like precision. In this acquisition of an instrumental task example, we can see that depending on the amount of training, different memory systems are engaged and control behavior based on what these systems do and what is needed early and later in training and probably because of different learning rate parameters of the different systems (see Gruber and McDonald, 2012 for experimental support for these claims).

Now what happens if the contingencies are changed or reversed for the rat after asymptotic performance is attained? In this case, the rat would now be reinforced for pulling the chain during light presentations and pressing the lever during tone presentations. In most instances like this, the rat will initially perseverate on the previous learned associations and then quickly return to chance levels of performance like their performance during the initial phases of training during acquisition. At this key point in reversal learning, it is likely that the emotional system is re-engaged and the rat continues to be motivated to obtain food, attends to the light and tone, and continues to make responses. The dorsomedial system would also be re-engaged. The re-engagement of the emotional system and the dorsomedial striatal goal-directed system is probably mediated via an executive decision by the prefrontal cortex because of unexpected lack of reinforcement in this specific internal (hungry) and external context (chamber, cues, and operandi). As training continues and enough reinforced trials have been experienced, the dorsolateral striatal habit system would take over again.

TRAIT DIFFERENCES INFLUENCING WHICH MEMORY SYSTEM GAINS BEHAVIORAL CONTROL IN A PARTICULAR INDIVIDUAL

Trait differences in rats have been reported on various behaviors including learning and memory (Hooks et al., 1994; Topic et al., 2005). These effects were reported on standard learning and memory tasks like the spatial version of the water maze. A different approach to this area of study is the use of Type B tasks, described in the previous section, to demonstrate traits differences in the ability of different learning and memory systems to gain access to behavior (McDonald and White, 1994). This was accomplished using a modified version of the water task (Sutherland and Rudy, 1988) in which rats were trained to navigate to a visible platform that was located in the same spatial position for 3 days and then trained on the 4th day to find a submerged platform in the same location. This training sequence was repeated thrice for a total of 12 days of training. On the 13th day, all subjects were given a choice between the original spatial location and the visible platform in a different location. Rats with damage to the hippocampus chose the visible platform and rats with damage to the dorsolateral striatum chose the

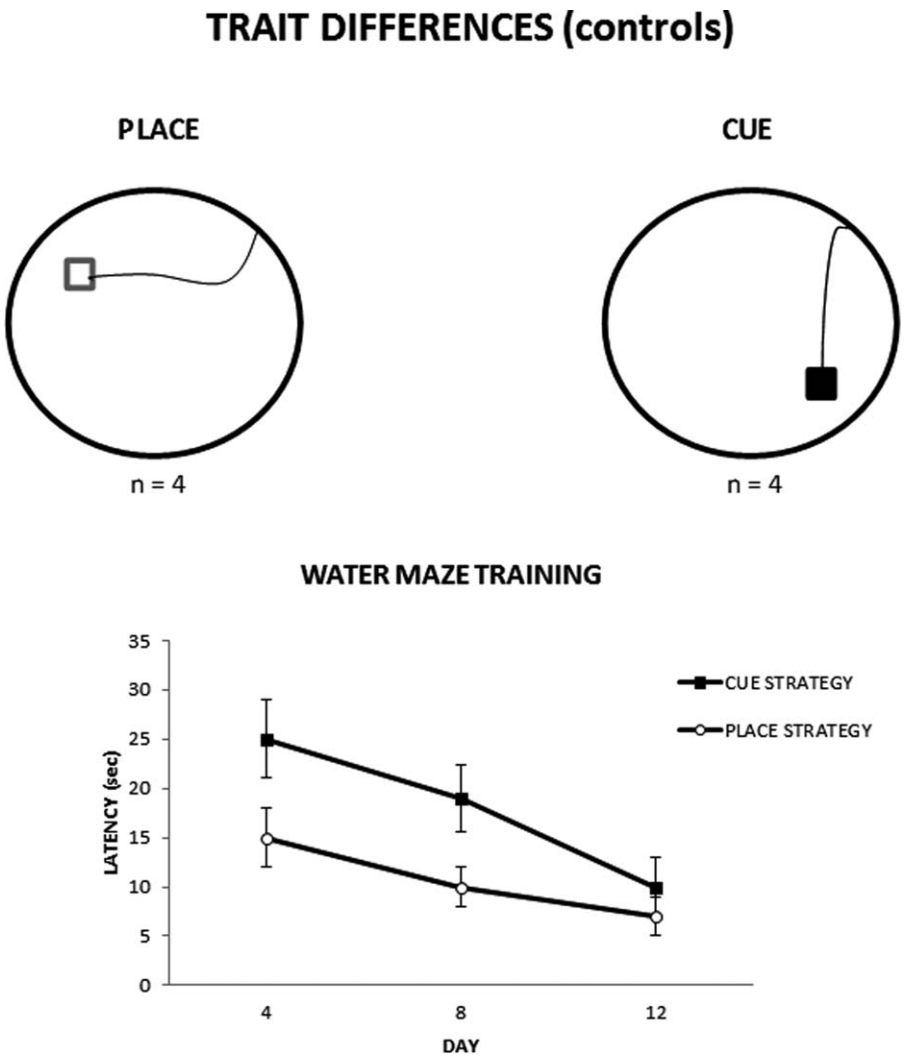

FIGURE 7. The swim patterns of control rats on a competition test. These rats had been previously trained on both cued and spatial trials to the same location. On the competition test, the subjects are given a choice between the visible cue in a new spatial location and the original spatial location. As can be seen, half of the control rats swam to the visible platform and the other half swam to the original spatial location (top panel). The rats that showed a spatial response during this test exhibited better place learning abilities during spatial training trials (bottom panel). This is an example of a trait difference mechanism determining which learning and memory system controls behavior in a multi-solution task [Figure adapted from McDonald and White, 1994].

original spatial location. More relevant to the current discussion, the control subjects split on this competition test. Half of the controls chose the visible platform and half chose the original spatial location (Fig. 7). An analysis of performance during training showed that the controls who chose the spatial location on the competition test were better place learners during original training suggesting that there were trait differences in the relative strength of these two learning and memory systems that determined which system gained control over behavior (Fig. 4).

These trait differences may emerge because of a complex set of interactions between an individual's: genetic make-up; developmental events during pre and post-natal time periods; and accumulated experience throughout the lifespan (McDonald et al., 2004). All of these factors can have major effects on the organization of the brain, and these alterations could affect overall relationships between each learning and memory system, as well as the relationships of these systems with the rest of the brain. For example, neural-based trait differences could be reflected in enhanced or inhibited plasticity in one learning and memory system compared to another (Colombo et al., 2003; Brightwell et al., 2008; Baudonnat et al., 2011). This difference in plasticity capability of one system over another would result in differences in associative strength during learning leading to behavioral control with the enhanced plasticity and loss or lack of control by a system with impoverished plasticity capabilities. This example makes the link between trait differences and associative strength mechanisms.

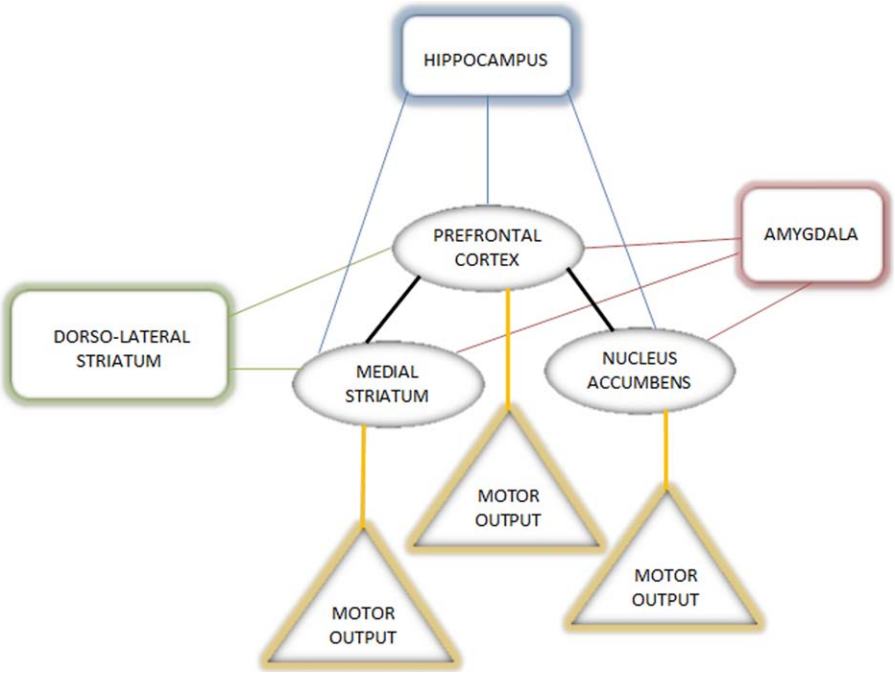

FIGURE 8. The medial striatum, the nucleus accumbens , and prefrontal cortex are common to the three learning and memory systems described in this article and are potential sites of interactions amongst them. These neural systems have access to motor output sites including various thalamic areas that project to supplementary, premotor, and prefrontal areas that can output to primary motor cortex and ultimately to the spinal cord. Note that the three memory systems can also access output nodes independent of the prefrontal cortex, medial striatum, and nucleus accumbens. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Neural-based trait differences could also be reflected in alterations in prefrontal cortex functions so that decision-making processes that utilize multiple memory representations, the subject's motivational state, and the current context might be compromised. This example links trait differences and important executive functions mediated by the prefrontal cortex.

In the next section, we will provide an example of trait differences that may account for differential memory system control in individuals trained on the same task under the same conditions.

TRAIT DIFFERENCES: EXAMPLES

Modulatory Neurotransmitter Systems

In a previous section, we reviewed research showing that differences in acetylcholine levels in different memory systems at different times of training can be correlated with which memory system was presumed to be controlling behavior (Chang and Gold, 2003). This control would be based on enhanced learning mechanisms related to the elevated cholinergic tone. Other work using similar paradigms and procedures showed that cholinergic release levels in the dorsolateral striatum is enhanced during acquisition of the plus-maze task in rats that exhibit response learning during the transfer test, and these neurotransmitter levels are enhanced in the hippocampus during acquisition in rats that exhibit place learning during the transfer test [(McIntyre et al., 2003); but see (Bizon et al., 2003)]. Interestingly, the rats exhibiting place responses on the transfer test showed enhanced acetylcholine release in the hippocampus even before training occurred, and the rats exhibiting the response strategy showed elevated acetylcholine release in the dorsal striatum even before training occurred. These results clearly show trait differences in a potential neurochemical mechanism for memory system control, elevated acetylcholine levels in the memory system that ultimately controls the subjects' behavior on a competition test.

POTENTIAL SITES OF INTERACTIONS BETWEEN MEMORY-BASED BEHAVIORAL SYSTEMS

One obvious set of neural sites for the interactions proposed in this article would be via direct projections from one system to another. For example, the hippocampus projects directly to the basolateral amygdala which provides a substrate for interactions between these systems. In fact, it is commonly thought that the hippocampus and amygdala interact during fear conditioning to context with the hippocampus forming a configural representation of the context and the amygdala providing

hippocampal access to unconditioned fear circuits (Rudy et al., 2004). This circuit is thought to control fear responses in the training context. Interestingly, if more training trials are given to the subjects the hippocampus is not necessary. This effect is thought to occur because the basolateral amygdala independently acquires a stimulus-affect representation that may be inhibited from controlling behavior when a hippocampal-amygdala representation is available (Lehmann et al., 2009; Sparks et al., 2011).

However, some of these systems do not have direct anatomical projections, so it must be the case that some of these interactions must occur in other commonly connected brain regions.

Figure 8 highlights potential neural sites in which the hippocampus, amygdala, and dorsal striatum might interact for memory-based control of behavior. These sites include the nucleus accumbens, prefrontal cortex, and the medial striatum. It is hypothesized that all of the proposed mechanisms discussed in this article involve interactions with these neural structures. In some cases, it is hypothesized that an interaction between learning and memory systems would occur at one of these sites and other interactions would recruit multiples or all of these structures in concert to gain control over behavior.

The nucleus accumbens is an interesting convergence node for the hippocampus, amygdala, and portions of the prefrontal cortex. It might be an area in which different representations from these memory systems might compete, using different mechanisms depending on the learning situation, for behavioral control.

For example, the nucleus accumbens is thought to be a central node of interaction between the hippocampus and amygdala during conditioned place preference learning. In this example, previous learning by the hippocampus may hinder amygdala access to the nucleus accumbens resulting in a reduction or blockade to potential routes for the amygdala to influence ongoing behavior. Increased hippocampal activity in the nucleus accumbens during pre-exposure to a context could also limit amygdala influence to ongoing behavior by reducing a dopamine-mediated "reward signal" available to the amygdala during appetitive classical conditioning procedures. The former would lead to an associative representation that is unable to access behavior, whereas the latter would impair associative processes in the amygdala reducing associative strength and limiting influence on behavior.

The prefrontal cortex is another site of potential interactions between the learning and memory systems because it receives input from all of them as well as information about the motivational state of the animal, the current situational context, and previous experiences that are similar (memory). Consistent with the idea that the prefrontal cortex makes a contribution to decisions about which learning and memory system and associated representation controls behavior (de Bruin et al., 1997; Ragozzino et al., 1999).

In contrast to the nucleus accumbens, the prefrontal cortex might be a system used for more reflective decisions in which multiple experiential iterations are required in which outcomes are recorded and the subject's behavior is modified based on this input. Another unique feature of the prefrontal system is that it might enable switching back and forth from one memory system representation to another based on changing information.

The medial striatum is an interesting brain region because it receives input from the hippocampus, amygdala, and prefrontal cortical sites as well as reciprocal projections to the dorsolateral portions of the striatum (McGeorge and Faull, 1989). We have argued that the medial striatum is a system involved in hippocampal control of behavior. For example, we have hypothesized that the medial striatum utilizes ventral hippocampal representations, like context-specific inhibitory associations, that influence changes in behavioral responses in dynamic learning situations like reversal learning. The medial striatal system is proposed to act in parallel to hippocampal-nucleus accumbens circuits so that damage to the medial striatum can enhance control of the nucleus accumbens circuit (McDonald et al., 2008). Information on how these parallel circuits influence the organization of memory-based behavior is not known.

CONCLUSIONS

One of the great challenges of systems neuroscience is to understand how different neural circuits involved in variants of associative learning and memory functions operate in the normal brain and how they contribute to control of voluntary action. According to the view presented in this article, there are different mechanisms that can influence which learning and memory system or systems elicits learned behavioral responses in a given situation. A clearer picture of human thought and behavior will emerge as more knowledge is acquired about how these systems interactions occur and when these processes are altered resulting in abnormal or pathological behavior.

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